Rescue effects of *Lactobacillus*-containing bismuth regimens after *Helicobacter pylori* treatment failure

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Abstract

At present, it has been scientifically proven that *Helicobacter pylori* is associated with gastrointestinal and extra-gastrointestinal diseases. Based to many studies, probiotics such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*, potentially are enable to reduce the severe clinical outcomes of gastrointestinal infections of this bacterium. Accordingly, the efficacy of *Lactobacillus*-containing bismuth quadruple therapy was measured by odds ratio with 95% confidence intervals. Overall, our statistical analysis results showed that *Lactobacillus*-containing bismuth quadruple therapy as rescue regimen, could have grater therapeutic effects during the treatment and eradication of *Helicobacter pylori* infection than non-probiotic treatment regimens in cases of treatment failure.

Keywords: *Helicobacter pylori*, *Lactobacillus*, MALT lymphoma, peptic ulcer, probiotics
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To the Editor,

Helicobacter pylori infection is one of the most important bacterial infections worldwide. Scientifically, this bacterium is associated with severe clinical outcomes including peptic ulcer, gastric cancer, mucosa-associated lymphoid tissue lymphoma, and various extragastrointestinal diseases [1,2]. Eradication of *H. pylori* infection has several benefits such as treatment of peptic ulcer diseases, prevention of recurrence of gastric cancer/mucosa-associated lymphoid tissue lymphoma in patients with history of endoscopic resections, and liver disorders [3]. However, eradicating *H. pylori* infection has become a challenging issue, especially in connection with the phenomenon of antibiotic resistance. In addition, high cost, incidence of side effects, and poor compliance with current treatment regimens have reduced the rate of *H. pylori* infection eradication in recent years [4,5]. As per the present guidelines, there are several regimens including (1) clarithromycin-based triple therapy (as the first-line therapy) for 14 days with proton pump inhibitors, clarithromycin, amoxicillin, or metronidazole in low clarithromycin-resistance areas, (2) bismuth quadruple therapy or levofloxacin triple therapy (as the second-line therapy), (3) nonbismuth quadruple therapy for 10–14 days plus proton pump inhibitors, clarithromycin, amoxicillin, and metronidazole, and (4) rifabutin-containing triple therapy (as the third-line therapy) [6]. Unfortunately, there is no treatment regimen associated with complete eradication (100%) of infection with this bacterium, so the World Health Organization also reports a high prevalence of *H. pylori* antibiotic resistance [7]. In recent years, the increasing incidence of *H. pylori* infection treatment failure has been a concern; interestingly, there is ample evidence that some probiotic bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* have anti–*H. pylori* activity during *in vitro* experiments [8]. García et al. [9] showed that coexistence of *Lactobacillus* and *H. pylori* in gastric biopsies of symptomatic patients was dramatically lower than in asymptomatic ones. In addition, Ojetti et al. [10] found that the curing rate in second-line treatment containing probiotic supplements increased by 18% with reduced side effects compared with that in second-line treatment only. Herein, we conducted this study to evaluate the clinical benefit of *Lactobacillus*-containing bismuth quadruple therapy to eradicate *H. pylori* infection in cases of treatment failure. We performed a computer-assisted literature search using several databases including PubMed, Scopus, and Google Scholar. Search terms included '*Helicobacter pylori*', '*H. pylori*', '*Lactobacillus*', 'Probiotics', and 'Treatment failure', with limitation in language and date. The full text of relevant documents was carefully evaluated. Required data including the first author, country, year, mean age, gender distribution, total cases, probiotics, rescue regimen, follow-up, eradication rate, and reference number are summarized in Table 1. The eradication rate was measured by event rate corresponding 95% confidence intervals (CIs). In addition, the efficacy of *Lactobacillus*-containing

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TABLE 1. Baseline characteristics of the included studies

First author	Country	Year	Mean age (years)		Male/female		Total cases		Probiotics	Rescue regimen	Follow-up time	Eradication rate		Reference
			Experiment	Control	Experiment	Control	Experiment	Control				Experiment	Control	
Sheu	Taiwan	2006	48.9	46.4	39/30	38/31	69	69	*L. acidobacillus*– and *Bifidobacterium*-containing yogurt	1 g of amoxicillin twice daily,500 mg of metronidazole twice daily, 20 mg of omeprazole twice daily, and 120 mg of bismuth subcitrate three times daily for 10 days	6 weeks UBT	Intention-to-treat analysis: 85.5% (77.2, 93.8) Per-protocol analysis: 90.8% (83.8, 97.8)	Intention-to-treat analysis: 71.1% (60.4, 81.8) Per-protocol analysis:76.6% (66.3, 86.9)	[12]
Dore	Italy	2019	54.1	54.1	16/33	13/37	49	50	2×10^8 CFU of *L. reuteri* DSM 17938 plus 2×10^8 CFU of *L. reuteri* ATCC PTA 6475	140 mg of bismuth subcitrate, 125 mg of metronidazole, and 125 mg of tetracycline for 10 days	4–6 weeks UBT	Per-protocol analysis: 95.7%; 95% CI = 85–99% Intention-to-treat analysis: 88%; 95% CI = 75–95%	Per-protocol analysis: 84.8%; 95% CI = 71–95% Intention-to-treat analysis: 79.6%; 95% CI = 65–89%	[13]
Wang	China	2014	NA	NA	NA	NA	90	90	*Lactobacillus acidophilus*	10 mg of rabeprazole bid + 1000 mg of amoxicillin bid + 100 mg of furazolidone bid + 300 mg of bismuth qid for 10 days	4 weeks UBT	Per-protocol analysis: 81.2% Intention-to-treat analysis: 76.7%	Per-protocol analysis: 78.2% Intention-to-treat analysis: 75.6%	[14]
Liu	China	2020	47.3	NA	17/33	NA	50	NA	*Lactobacillus acidophilus*, 2.5×10^6 cells of *Streptococcus faecalis*, and 5×10^3 cells of *Bacillus subtilis*	Esomeprazole (20 mg, bid), bismuth potassiumcitrate (220 mg, bid), tetracycline (750 mg, bid),and furazolidone (100 mg, bid) for 10 days	4 weeks UBT	Intention-to-treat analysis: 92.0 (84.0–98.0) Per-protocol analysis: 91.8 (83.7–98.0)	NA	[15]

CI, confidence interval; UBT, urea breath test.

bismuth quadruple therapy was evaluated by odds ratio (OR) with 95% CIs. Heterogeneity was assessed by the I^2 index and Cochrane-*Q* value. Publication bias was also calculated using Begg's *p* value and Egger's *p* value test [11]. In general, there were four studies as per our criteria that were conducted in Italy, Taiwan, and China during the years 2006–2020. We entered data of 467 patients (mean age: 50.16 years; male percentage: 26.3%) in the present study. These patients had received a *Lactobacillus*-containing bismuth quadruple therapy for 10 days. In all eligible studies, curing *H. pylori* infection had been evaluated by urea breath test after 4–6 weeks [12–15]. As per intention-to-treat analysis, the eradication rate of infection in patients with *Lactobacillus*-containing bismuth quadruple therapy and control subjects was estimated to be 83.2% (95% CI: 77.9–87.4; I^2: 52.4; *Q*-value: 6.3; Begg's *p* value: 0.89; Egger's *p* value: 0.01) and 75% (95% CI: 0.00; I^2:0.00; *Q*-value: 1.25; Begg's *p* value: 34; Egger's *p* value: 0.52), respectively. In addition, based on the per-protocol analysis, the eradication rate in both *Lactobacillus*-containing bismuth quadruple therapy and control groups was 87% (95% CI: 81.9–90.8; I^2: 57.7; *Q*-value: 7.1; Begg's *p* value: 0.08; Egger's *p* value: 0.01) and 78.8% (95% CI: 72.7–83.8; I^2: 0.0; *Q*-value: 1.0; Begg's *p* value: 0.5; Egger's *p* value: 0.27), respectively. Our results suggested that the eradication rate of *H. pylori* infection was significantly higher in the *Lactobacillus*-containing bismuth quadruple therapy group than control subjects based on intention-to-treat analysis (OR: 1.77; 95% CI: 1.11–2.83; *p* value: 0.01; I^2: 0.00; *Q*-value: 0.78; Begg's *p* value: 0.5; Egger's *p* value: 0.64) and per-protocol analysis (OR: 2.08; 95% CI: 1.23–3.52; *p* value: 0.01; I^2: 0.0; *Q*-value: 1.56; Begg's *p* value: 0.29; Egger's *p* value: 0.17). In the present documents, we revealed that probiotic supplementation can increase the cure rate about 8.2% greater than standard bismuth quadruple therapy. It seems that probiotic supplementation has clinical benefits in raising the eradication rate of *H. pylori* infection in treatment failure cases. As per the literature, there are several hypotheses that explain how probiotic therapy has clinical benefits in curing *H. pylori* infection including (1) direct antagonism between *H. pylori* and *Lactobacillus* and *Bifidobacterium* in establishing the long-term colonization of *H. pylori* in the stomach [16,17], (2) *Lactobacillus* spp. inhibiting attachment of *H. pylori* into the gastric epithelium [18], (3) *Lactobacillus* and *Bifidobacterium* provoking immune response against *H. pylori* [19], (4) continued intake of *Bifidobacterium*-containing diet leading to decrease in hydrogen production and thus lower density of *H. pylori* colonization [20], and (5) direct inhibition of urease production after gastric colonization by *Lactobacillus and Bifidobacterium* hampering stable colonization of *H. pylori* [21]. Zheng et al. [22] published a meta-analysis on the clinical efficacy of *Lactobacillus*-containing probiotic supplementation for the eradication of *H. pylori* infection; they concluded that probiotic supplementation significantly increased the cure rate of *H. pylori* infection (risk ratio: 1.14; 95% CI: 1.06–1.22). We also confirmed the benefits of bismuth rescue diets containing *Lactobacillus* to achieve higher eradication rates in cases of treatment failure. However, as per the criteria by Graham et al. [23], successful treatment was defined for the intention-to-treat regimen with eradication rate ≥90%, treatment failure was defined for cases with per-protocol cure rate <90%. Therefore, *Lactobacillus*-containing bismuth as the rescue regimen has an acceptable borderline for the treatment of *H. pylori* infection in cases of treatment failure; but we should suggest that probiotic-containing regimens have been associated with a higher cure rate and need to be optimized in further investigations.

Transparency declaration

The authors have no conflict of interest.

Abbreviation list

H. pylori *Helicobacter pylori*
MALT mucosa-associated lymphoid tissue
PPIs proton pump inhibitors
WHO World Health Organization
OR odds ratio
CIs confidence intervals
UBT urea breath test

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